PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gunnar Leo KARUP, et al.

Docket No: Q86966

Appln. No.: 10/528,691

Group Art Unit: 1625

Confirmation No.: 4613

Examiner: Celia C. Chang

Filed: March 22, 2005

For: NOVEL RALOXIFENE ACID ADDITION SALTS AND/OR SOLVENTS THEREOF, IMPROVED METHOD FOR PURIFICATION OF SAID RALOXIFENE ACID ADDITION SALTS AND/OR SOLVATES THEROF AND PHARMACEUTICAL COMPOSITION COMPRISING THESE

DECLARATION UNDER 37 C.F.R. § 1.132

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Erik Fischer, hereby declare and state:

THAT I am a citizen of Denmark;

THAT I have received the degree of M.Sc. Chemistry in 1994 from the University of Copenhagen;

THAT I have been employed as a scientist by Medico Chemical Laboratory/Riso National Laboratory in Denmark from February 1995 to October 1995;

THAT I have been employed at Novo Nordic A/S.

THAT I have been employed at GEA Farmaceutisk Fabrik (now Pharmazell Denmark A/S), since August 98, the last six years as head of chemical development;

THAT I was part of the development team associated with the above-identified application when it was discovered that the name of the compounds of Examples 4 and 6 -

Raloxifene DL-lactate hemihydrate and Raloxifene L-lactate ¼-hydrate, respectively, were incorrect;

THAT I was part of the development team associated with the above-identified application when it was discovered that the correct name of the compounds of Examples 4 and 6 are Raloxifene DL-lactate and Raloxifene L-lactate, respectively;

THAT the error was discovered as a result of the newest development within the area of analysis techniques;

THAT, on November 29, 2006, it was discovered that Raloxifene DL-lactate was the anhydrate, as shown by the lab report and corresponding differential scanning calorimetric chart attached as Exhibit A;

THAT, shortly after December 6, 2006, it was discovered that Raloxifene ¼ hydrate was the anhydrate, based on the results that the water content was 0.4%, as shown by the lab report attached as Exhibit B.

THAT the inventors were in possession of Raloxifene DL-lactate and Raloxifene L-lactate, as identified by the X-ray diffraction pattern provided below on September 30, 2002 (filing date of the priority application (PA 200201450)), at the latest;

THAT, at the latest, on September 30, 2002, the inventors were in possession of a compound exhibiting the following X-ray crystalline positions,

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
13.595814	6.4959	28.40	12683	0.1400
10.855533	8.1382	16.15	7211	0.1200
9.849394	8.9711	32.17	14369	0.1000
9.534325	9.2682	66.95	29898	0.1300

8.150249	10.8465	45.20	20188	0.1300
7.240730	12.2138	63.53	28374	0.1400
6.769843	13.0670	18.42	8227	0.1500
6.272666	14.1077	75.67	33794	0.1900
5.818832	15.2143	13.28	5933	0.2000
5.657337	15.6513	18.07	8070	0.1300
5.505030	16.0872	10.51	4692	0.1000
5.261933	16.8357	17.48	7806	0.1400
5.089504	17.4104	16.14	7210	0.1000
5.001569	17.7189	41.94	18732	0.0900
4.958950	17.8725	29.16	13023	0.1148
4.797388	18.4795	19.39	8660	0.1100
4.669322	18.9910	49.20	21972	0.1400
4.574684	19.3876	63.21	28227	0.1000
4.533019	19.5676	44.94	20071	0.1148
4.440548	19.9792	32.70	14604	0.1200
4.301886	20.6301	100.00	44659	0.1500
4.155406	21.3657	78.00	34833	0.1600
4.059049	21.8797	27.53	12296	0.1800
3.960846	22.4285	25.59	11427	0.1000
3.907408	22.7393	83.48	37282	0.1200
3.865461	22.9894	16.46	7350	0.1148
3.828892	23.2120	17.46	7798	0.0900
3.773130	23.5599	50.71	22649	0.1200

3.716486	23.9243	23.06	10300	0.1300
3.652238	24.3515	15.79	7053	0.1800
3.584725	24.8174	12.91	5764	0.1500
3.486791	25.5261	30.45	13600	0.1200
3.439149	25.8858	22.21	9919	0.1300
3.396267	26.2184	17.86	7978	0.1100
3.370045	26.4261	12.48	5572	0.1148
3.329320	26.7553	9.21	4113	0.1100
3.292728	27.0582	11.81	5274	0.1000
3.278070	27.1815	11.25	5026	0.1148
3.218620	27.6935	21.24	9485	0.1900
3.167986	28.1452	13.80	6162	0.0900
3.143230	28.3715	30.33	13546	0.1000
3.095423	28.9191	14.02	6260	0.1200
3.024921	29.5058	11.56	5161	0.1400
3.007253	29.6831	13.40	5984	0.1300

and exhibiting a mp of 196-198°C, having an IR spectra, and elemental analysis of 65.07% C, 5.93% H, 2.37% N, and 5.34% S as set forth on page 22 of the specification;

THAT, at the latest, on September 30, 2002, the inventors were in possession of a compound exhibiting the following X-ray crystalline positions,

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
14.079244	6.2726	45.93	16568	0.1300
9.974912	8.8580	32.43	11699	0.1100

9.526523	9.2758	71.31	25721	0.1200
8.215598	10.7600	47.82	17248	0.1100
7.246270	12.2045	80.04	28871	0.1100
7.065557	12.5178	16.17	5832	0.0700
6.878001	12.8606	22.74	8201	0.1200
6.283709	14.0828	66.27	23901	0.0800
6.194698	14.2862	53.98	19470	0.0984
5.859529	15.1080	11.17	4028	0.0984
5.744935	15.4112	16.16	5828	0.1200
5.312222	16.6751	18.02	6499	0.1200
5.046910	17.5585	34.26	12356	0.0900
4.978933	17.8001	54.66	19715	0.1000
4.918535	18.0205	17.40	6277	0.0984
4.746264	18.6804	26.77	9655	0.1000
4.712771	18.8143	46.35	16716	0.0900
4.569429	19.4101	57.60	20777	0.1000
4.455985	19.9093	53.60	19332	0.1200
4.345589	20.4204	12.70	4579	0.0900
4.268096	20.7952	86.33	31139	0.0900
4.106332	21.6241	20.17	7274	0.1100
4.042283	21.9710	22.73	8197	0.1200
3.944656	22.5218	23.46	8462	0.1000
3.913129	22.7056	100.00	36069	0.1100
3.831706	23.1947	15.49	5586	0.0900

3.777075	23.5350	69.72	25148	0.1400
3.735872	23.7983	14.85	5358	0.0984
3.667856	24.2463	11.94	4305	0.0900
3.639035	24.4413	13.87	5001	0.0800
3.589918	24.7809	9.38	3383	0.0984
3.545715	25.0949	23.58	8505	0.0800
3.505655	25.3864	33.63	12131	0.1100
3.442223	25.8622	22.60	8152	0.1100
3.411017	26.1030	10.82	3901	0.0984
3.371851	26.4117	44.16	5108	0.1000
3.280618	27.1600	15.23	5494	0.1100
3.251104	27.4114	14.23	5134	0.0800
3.232072	27.5760	19.25	6943	0.1100
3.153056	28.2812	12.42	4479	0.1900
3.143130	28.3724	12.29	4432	0.0984
3.081939	28.9479	17.16	6189	0.2200
3.040378	29.3524	9.73	3510	0.1300
2.990508	29.8532	15.29	5514	0.1400
2.929711	30.4876	11.37	4102	0.1200
2.892397	30.8906	18.91	6822	0.1200
2.856192	31.2922	8.91	3214	0.1100
2.818108	31.7261	14.79	5336	0.2500
2.765584	32.3450	15.86	5720	0.1300

and exhibiting a mp of 171-173°C, having an IR spectra, and elemental analysis of 65.50% C, 5.85% H, 2.50% N, and 5.74% S as set forth on page 29 of the specification;

THAT the above compounds are the compounds of Examples 4 and 6, respectively;

THAT on September 30, 2002, at the latest, the inventors were in possession of the compounds of Examples 4 and 6 of the specification, which are Raloxifene DL-lactate and Raloxifene L-lactate, respectively, which is demonstrated by the X-ray diffraction patterns (Figures 2 and 6 of the present application) and reproduced below;

Figure 2 of the present application

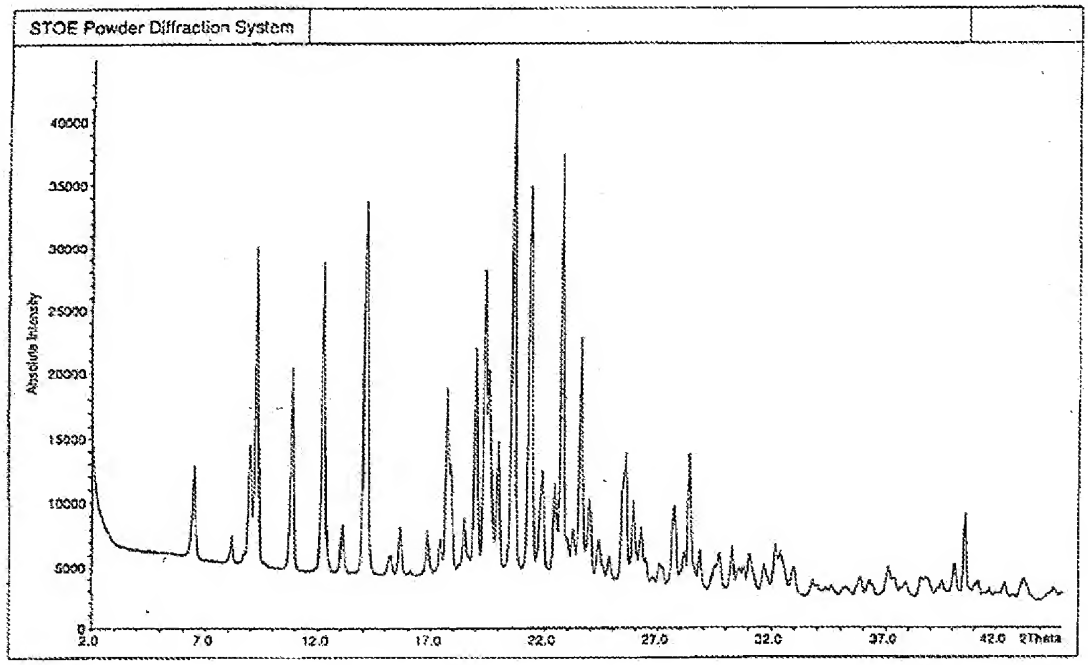
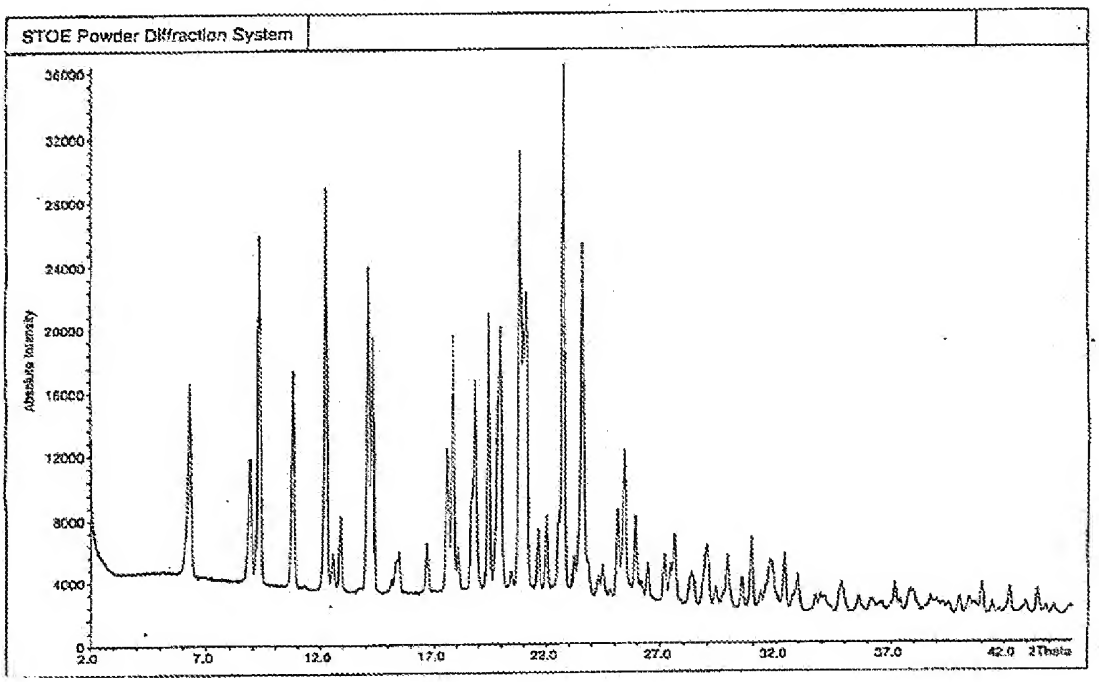


Figure 6 of the present application



THAT samples #6.4045.23.1 (Raloxifene DL-lactate) and #6.4045.24.1 (Raloxifene L-lactate) were prepared according to the processes of Examples 4 and 6, respectively.

THAT the X-ray diffraction patterns for Raloxifene DL-lactate and Raloxifene L-lactate, obtained according to the process for preparing the compounds of Examples 4 and 6, were obtained using Siemens D-5000 diffractometer (Bruker-AXS, Karlsruhe, Germany).

THAT when the X-ray diffraction pattern of Figure 2 of the present application and for Raloxifene DL-lactate above, and Figure 6 of the present application and for Raloxifene L-lactate were superimposed, there was very good compliance, as can be seen below.

Figure A Superimposition of XRPD-diffractogram for #6.4045.23.1[1]

[1] The arrows point to two minor differences thought to represent impurities in the analyzed sample.

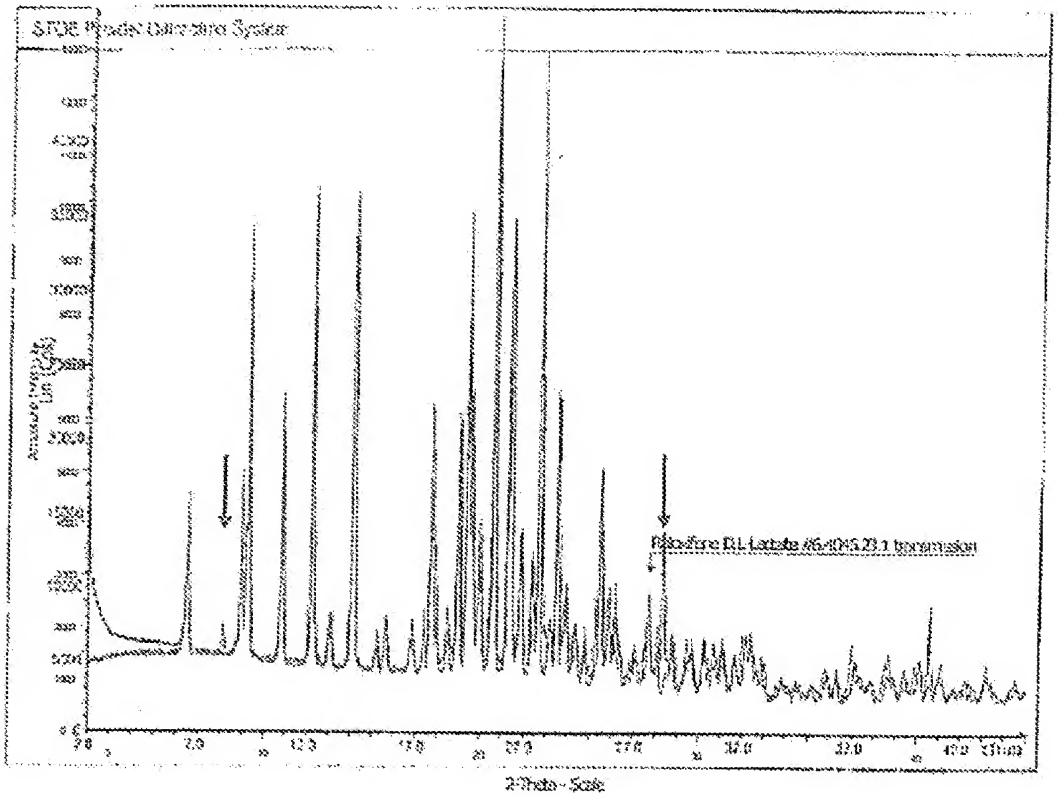
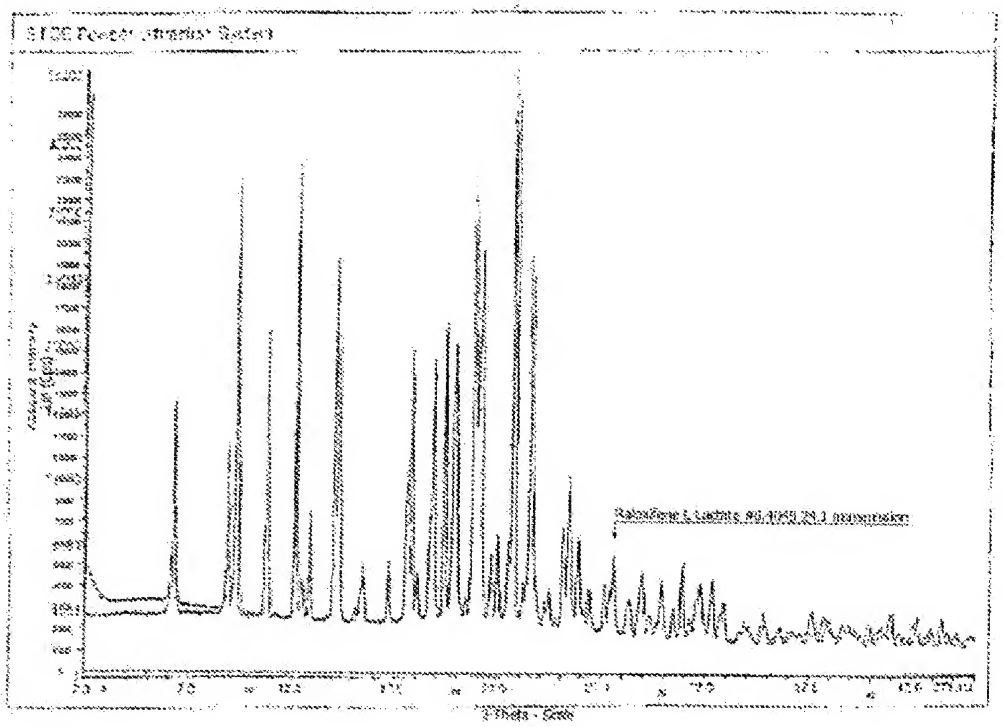


Figure B Superimposition of XRPD-diffractogram for #6.4045.24.1



THAT it is well known that if X-ray diffraction patterns are identical, the samples must be of identical crystalline structure and hydratization;

THAT since the X-ray diffraction patterns of Example 4 of the specification and #6.4045.23.1 (Raloxifene DL-lactate) are identical, it is evident that the inventors had possession of Raloxifene DL-lactate on September 30, 2002, at the latest;

THAT since the XRPD patterns of Example 6 of the specification and #6.4045.24.1 (Raloxifene L-lactate) are identical, it is evident that the inventors had possession of Raloxifene L-lactate on September 30, 2002, at the latest;

THAT it is also evident that the compounds described as "D, L-lactate hemihydrate" or "L-lactate ¼ -hydrate" in the present specification were anhydrous; and

THAT new compounds are not being introduced into the present application, but only the name of the compounds of Examples 4 and 6 are being corrected.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12.10.2010

Erik Fischer